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## 14-day Oral Dose Range Finding Study in Rats

with

**WACKER BS 1701**

Study Director: Dr. Achim Albrecht

Date of Report: 14.11.2000

### Short-Report

**BSL BIOSERVICE Project No.: 001698**

#### Sponsor

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*Werk Burghausen*

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ZLG-P-986.96.01

**CONTENTS**

	page
<b>PREFACE</b>	<b>3</b>
General	3
Project Staff	3
Schedule	3
Project Staff Signatures	4
Guidelines	4
Archiving	4
<b>SUMMARY</b>	<b>5</b>
Conclusions	5
<b>INTRODUCTION</b>	<b>6</b>
<b>MATERIALS AND METHODS</b>	<b>7</b>
Characterisation of the Test Item	7
Preparation of the Test Item	7
Administration of Doses	8
Test Animals	8
Animal Husbandry	8
Body Weight Development	9
Clinical Observation	9
Blood Sampling	9
Haematology and Clinical Biochemistry	10
Pathology	11
<b>RESULTS</b>	<b>12</b>
Body Weight Development	12
Food Consumption	28
Clinical Observation	28
Haematology and Clinical Biochemistry	28
Pathology	29
<b>RESULTS</b>	<b>30</b>
Conclusions	31
<b>DISTRIBUTION OF THE REPORT</b>	<b>32</b>

## Preface

### *General*

Sponsor: Wacker-Chemie GmbH  
Werk Burghausen  
Johannes-Hess-Strasse 24  
D-84489 Burghausen, Germany

Monitor: Dr. Axel Bosch

Testing Facility: BSL BIOSERVICE Scientific  
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Behringstrasse 6  
D-82152 Planegg/München

BSL BIOSERVICE-  
Project No.: 001698

Test Item: WACKER BS 1701

Title: 14-day Oral Dose Range Finding Study in  
Rats  
with WACKER BS 1701

### *Project Staff*

Study Director: Dr. Achim Albrecht

Deputy Director of the  
Testing Facility: Dr. Angela Lutterbach

Quality Assurance Unit: Dr. Margarete Hoechst  
Dipl. Biol. Maike Führböter

### *Schedule*

Arrival of Test Item: 26.10.2000  
Start of Study: 30.10.2000  
End of Study: 14.11.2000

Date of Short-Report: 14.11.2000

*Project Staff Signatures*

Study Director:

Dr. Achim Albrecht

  
.....

Date: 14.11.2000

Deputy Director of the  
Testing Facility:

Dr. Angela Lutterbach

  
.....

Date: 14.11.2000

*Guidelines*

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

Under consideration of:

First Addendum to OECD Guidelines for Testing of Chemicals, Section 4, No.407, "Repeated Dose 28-day Oral Toxicity Study in Rodents" adopted 27 July, 1995.

Directive 96/54 EEC B.7.

*Archiving*

All original data generated during the conduct of the study (raw data, copy of report) will be stored in the Scientific Archives of BSL BIOSERVICE Scientific Laboratories GmbH for 12 years after issue of the report.

## Summary

In this 14-day Oral Dose Range Finding Study with the test item WACKER BS 1701 no specific compound related effects were observed.

The test item was orally administered in graduated doses to three groups of male and female rats (HSDBrl:WH Wistar) by gavage, using a stomach tube.

Totally 14 applications per animal were administered.

The following doses were chosen:

- 500 mg/kg BW
- 1000 mg/kg BW
- 2000 mg/kg BW

The volume of application was 5 ml/kg BW.

All rats survived throughout the test period without showing relevant clinical-toxic effects and were sacrificed on day 14.

No relevant differences in weight gain between the 3 dosed groups could be detected in male and female animals.

All animals showed normal food intake and no obvious reduction in food consumption was found.

Most haematology and clinical biochemistry-values were within the expected ranges. No relevant differences between the groups were found. No dose dependency and toxicological relevance was found.

## Conclusions

Considering the reported data the following doses are recommended for the 28 day Toxicity study:

- Low Dose: 150 mg/kg BW
- Medium Dose: 500 mg/kg BW
- High Dose: 1000 mg/kg BW

## **Introduction**

In the assessment and evaluation of the toxic characteristics of chemicals, the determination of oral toxicity using repeated doses may be carried out after initial information on toxicity which has been obtained by acute testing.

The purpose of this study was to obtain information on the toxic potential of the test item in rats in order to establish a suitable dose regimen for a 28-day oral toxicity study.

## Materials and Methods

### *Characterisation of the Test Item*

The test item and the information concerning the test item were provided by the sponsor.

Name:	Wacker BS 1701
Chemical description:	Alkylalkoxysilane
Batch No.:	KH 02343
CAS.-No.:	35435-21-3
Aggregate State at RT:	liquid
Colour:	colourless
Density (g/cm <sup>3</sup> ):	0.86 at 25°C
Purity:	98.53%
Analysis:	GC
Stability:	Pure: years Stable in aqueous solution for at least 24 hours
Storage:	at room temperature, protected from light
Expiry Date:	November 2001
Safety Precautions	Routine hygienic procedures were sufficient to assure personnel health and safety.

### *Preparation of the Test Item*

The test item was suspended in Carboxymethylcellulose, CMC, (SIGMA-ALDRICH CHEMIE GmbH, D-82041 Deisenhofen; lot 36H0738) (1% in aqua.). The vehicle was chosen due to its non-toxic characteristics.

The following dosages were prepared :

- 500 mg/kg BW
- 1000 mg/kg BW
- 2000 mg/kg BW

### *Administration of Doses*

The animals were dosed with the test item on 7 days per week for a period of 14 days by gavage, using a stomach tube.

Volume of application: The different doses were applied according to body-weight at a volume of 5ml/kg BW.

### *Test Animals*

Species: Hsd:Wistar rats (HsdBrl:WH,Full-Barrier)

Supplier: Harlan Winkelmann GmbH, D-33178 Borcheln. The animals were derived from a controlled full barrier maintained breeding system (spf).

Health status: No special findings during the adaptation period; females nulliparous, non-pregnant.

Number and

Sex: 3 female and 3 male rats were evaluated at the dose levels 500 and 1000 mg/kg BW. At 2000 mg/kg BW one female and one male animal was dosed.

According to Art. 9.2, No.7 of the German Act on Animal Welfare the animals were bred for experimental purposes.

### *Animal Husbandry*

The animals were barrier maintained (semi-barrier) in air conditioned rooms

- Temperature:  $22 \pm 3^{\circ}$  C
- Rel. humidity:  $55 \pm 10\%$
- Artificial light, lighting regime 12 : 12 hours, light 6.30 - 18.30
- Air change: at least 10 x / hour
- Feeding ad libitum, Altromin 1324 maintenance diet for rats and mice, totally-pathogen-free-TPF
- Free access to tap water (drinking water, municipal residue control, microbiol. controlled periodically)
- The animals were individually kept in Macrolon cages on Altromin saw fiber bedding
- Adequate Acclimatization period

Table 1: Dose groups

Group	Dose of test item (mg/kg BW)	Female rats No.	Male rats No.
1	500	9, 10, 12	7, 8, 11
2	1000	4, 5, 6	1, 2, 3
3	2000	B	A

### *Body Weight Development*

The animals were weighed prior to first application (day 0) and once a day thereafter.

### *Clinical Observation*

The observation period was 14 days. General clinical observations were made at least once a day, preferably at the same time each. The health condition of the animals was recorded. At least twice daily, all animals were observed for morbidity and mortality.

Cageside observations included spontaneous activity, lethargy, recumbent position, convulsions, tremors, apnoe, asphyxia, vocalisation, diarrhoea, changes in the skin and fur, eyes and mucous membranes (salivation, discharge), piloerection and pupil size.

### *Blood Sampling*

The withdrawal of blood was performed by puncture of the abdominal aorta of the anaesthetized animals. This was part of the procedure of killing the animals on the day of necropsy.

The blood was collected into small tubes containing EDTA for haematology, citrat for clotting tests and plain tubes for clinical biochemistry.

## *Haematology and Clinical Biochemistry*

The following parameters were determined for evaluation:

Haematology:

Haemoglobin, Haematocrit, Red Blood Cell Count, White Blood Cell Count, Platelets.

Clinical Biochemistry:

GOT, GPT, Glucose, Urea, Creatinine

### *Pathology*

All animals in the study were subjected to a full, detailed gross necropsy which included careful examination of the external surface of the body, all orifices and the cranial, thoracic and abdominal cavities and their contents.

# Results

## Body Weight Development

No relevant differences in weight gain between the 3 dosed groups could be detected in male and female animals.

### Individual Body weight development male animals:

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
1	male	1000	204			
		1000	209	5	5	2000
		1000	214	5	10	3000
		1000	219	5	15	4000
		1000	227	8	23	5000
		1000	224	-3	20	6000
		1000	229	5	25	7000
		1000	240	11	36	8000
		1000	246	6	42	9000
		1000	250	4	46	10000
		1000	254	4	50	11000
		1000	262	8	58	12000
		1000	266	4	62	13000
		1000	268	2	64	14000

#### Weight Development

Application	Weight (g)
1	204
2	209
3	214
4	219
5	227
6	224
7	229
8	240
9	246
10	250
11	254
12	262
13	266
14	268

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
2	male	1000	200			
		1000	208	8	8	2000
		1000	214	6	14	3000
		1000	217	3	17	4000
		1000	228	11	28	5000
		1000	224	-4	24	6000
		1000	229	5	29	7000
		1000	240	11	40	8000
		1000	246	6	46	9000
		1000	252	6	52	10000
		1000	256	4	56	11000
		1000	262	6	62	12000
		1000	262	0	62	13000
		1000	265	3	65	14000

### Weight Development

Application	Weight (g)
1	200
2	208
3	214
4	217
5	228
6	224
7	229
8	240
9	246
10	252
11	256
12	262
13	262
14	265

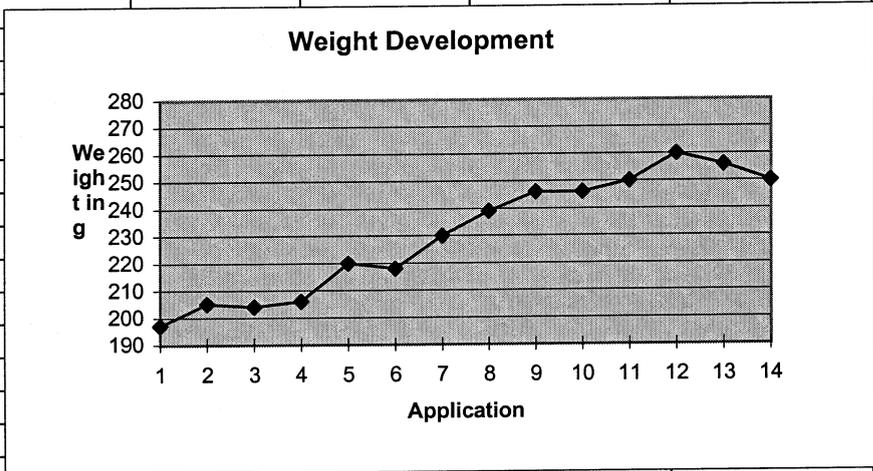
001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
3	male	1000	214			
		1000	220	6	6	2000
		1000	226	6	12	3000
		1000	232	6	18	4000
		1000	242	10	28	5000
		1000	238	-4	24	6000
		1000	243	5	29	7000
		1000	248	5	34	8000
		1000	256	8	42	9000
		1000	262	6	48	10000
		1000	268	6	54	11000
		1000	272	4	58	12000
		1000	274	2	60	13000
		1000	274	0	60	14000

**Weight Development**

Application	Weight (g)
1	214
2	220
3	226
4	232
5	242
6	238
7	243
8	248
9	256
10	262
11	268
12	272
13	274
14	274

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
7	male	500	197			
		500	205	8	8	1000
		500	204	-1	7	1500
		500	206	2	9	2000
		500	220	14	23	2500
		500	218	-2	21	3000
		500	230	12	33	3500
		500	239	9	42	4000
		500	246	7	49	4500
		500	246	0	49	5000
		500	250	4	53	5500
		500	260	10	63	6000
		500	256	-4	59	6500
		500	250	-6	53	7000





001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
11	male	500	154			
		500	166	12	12	1000
		500	176	10	22	1500
		500	184	8	30	2000
		500	192	8	38	2500
		500	205	13	51	3000
		500	205	0	51	3500
		500	208	3	54	4000
		500	216	8	62	4500
		500	226	10	72	5000
		500	230	4	76	5500
		500	236	6	82	6000
		500	240	4	86	6500
		500	242	2	88	7000

### Weight Development

Application	Weight (g)
1	154
2	166
3	176
4	184
5	192
6	205
7	205
8	208
9	216
10	226
11	230
12	236
13	240
14	242

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
A	male	2000	206			
		2000	211	5	5	4000
		2000	202	-9	-4	6000
		2000	202	0	-4	8000
		2000	196	-6	-10	10000
		2000	200	4	-6	12000
		2000	215	15	9	14000
		2000	230	15	24	16000
		2000	240	10	34	18000
		2000	246	6	40	20000
		2000	256	10	50	22000
		2000	260	4	54	24000
		2000	266	6	60	26000
		2000	268	2	62	28000

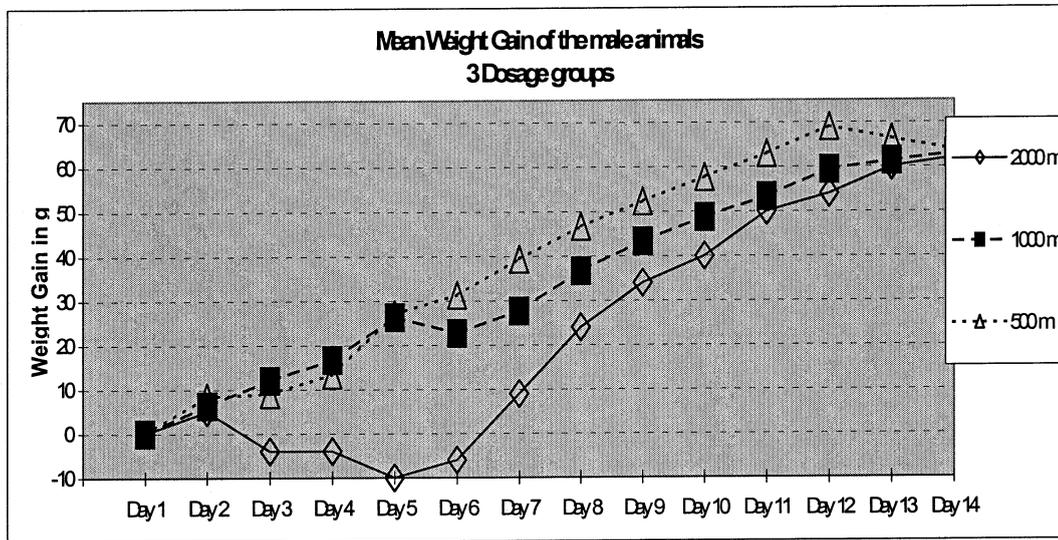
  

### Weight Development

Application	Weight (g)
1	206
2	211
3	202
4	202
5	196
6	200
7	215
8	230
9	240
10	246
11	256
12	260
13	266
14	268

**Mean Body weight development male animals:**

Mean Body Weight Males		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Dosage	Sex														
2000m	m	0,00	5	-4	-4,0	-10	-6	9	24	34	40	50	54	60	62
1000m	m	0,00	6,33	12,0	16,67	26,33	22,67	27,67	36,67	43,33	48,67	53,33	59,33	61,33	63
500m	m	0,00	8,33	9	13,33	27	31,33	39,33	46,67	52,33	57,67	63	69	66,33	63,67



**Individual Body weight development female animals:**

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
4	female	1000	170			
		1000	170	0	0	2000
		1000	165	-5	-5	3000
		1000	174	9	4	4000
		1000	180	6	10	5000
		1000	182	2	12	6000
		1000	182	0	12	7000
		1000	182	0	12	8000
		1000	186	4	16	9000
		1000	186	0	16	10000
		1000	184	-2	14	11000
		1000	188	4	18	12000
		1000	192	4	22	13000
		1000	190	-2	20	14000

**Weight Development**

Application	Weight (g)
1	170
2	170
3	165
4	175
5	180
6	182
7	182
8	182
9	186
10	186
11	184
12	188
13	192
14	190

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
5	female	1000	160			
		1000	166	6	6	2000
		1000	158	-8	-2	3000
		1000	167	9	7	4000
		1000	168	1	8	5000
		1000	168	0	8	6000
		1000	170	2	10	7000
		1000	172	2	12	8000
		1000	174	2	14	9000
		1000	180	6	20	10000
		1000	180	0	20	11000
		1000	176	-4	16	12000
		1000	178	2	18	13000
		1000	180	2	20	<b>14000</b>

### Weight Development

Application	Weight (g)
1	160
2	166
3	158
4	167
5	168
6	168
7	170
8	172
9	174
10	180
11	180
12	176
13	178
14	180

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
6	female	1000	152			
		1000	153	1	1	2000
		1000	153	0	1	3000
		1000	160	7	8	4000
		1000	160	0	8	5000
		1000	161	1	9	6000
		1000	160	-1	8	7000
		1000	164	4	12	8000
		1000	166	2	14	9000
		1000	166	0	14	10000
		1000	166	0	14	11000
		1000	168	2	16	12000
		1000	168	0	16	13000
		1000	170	2	18	14000

### Weight Development

Application	Weight (g)
1	152
2	153
3	153
4	160
5	160
6	161
7	160
8	164
9	166
10	166
11	166
12	168
13	168
14	170

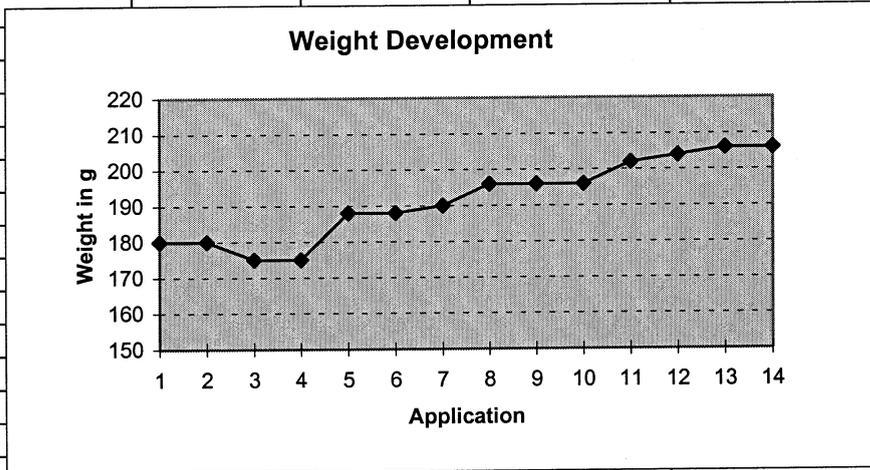
001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
9	female	500	159			
		500	163	4	4	1000
		500	151	-12	-8	1500
		500	151	0	-8	2000
		500	165	14	6	2500
		500	168	3	9	3000
		500	168	0	9	3500
		500	177	9	18	4000
		500	182	5	23	4500
		500	180	-2	21	5000
		500	186	6	27	5500
		500	190	4	31	6000
		500	192	2	33	6500
		500	190	-2	31	<b>7000</b>

### Weight Development

Application	Weight (g)
1	159
2	163
3	151
4	151
5	165
6	168
7	168
8	177
9	182
10	180
11	186
12	190
13	192
14	190

No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
10	female	500	180			
		500	180	0	0	1000
		500	175	-5	-5	1500
		500	175	0	-5	2000
		500	188	13	8	2500
		500	188	0	8	3000
		500	190	2	10	3500
		500	196	6	16	4000
		500	196	0	16	4500
		500	196	0	16	5000
		500	202	6	22	5500
		500	204	2	24	6000
		500	206	2	26	6500
		500	206	0	26	<b>7000</b>



001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
12	female	500	150			
		500	152	2	2	1000
		500	158	6	8	1500
		500	162	4	12	2000
		500	160	-2	10	2500
		500	164	4	14	3000
		500	164	0	14	3500
		500	170	6	20	4000
		500	172	2	22	4500
		500	178	6	28	5000
		500	178	0	28	5500
		500	180	2	30	6000
		500	182	2	32	6500
		500	189	7	39	7000

### Weight Development

Application	Weight (g)
1	150
2	152
3	158
4	162
5	160
6	164
7	164
8	170
9	172
10	178
11	178
12	180
13	182
14	189

001698						
No.	Sex	Dosage mg/kg	weight g	weight Development daily	weight Development Sum.	Dosage Sum.
B	female	2000	164			
		2000	168	4	4	4000
		2000	164	-4	0	6000
		2000	170	6	6	8000
		2000	178	8	14	10000
		2000	180	2	16	12000
		2000	179	-1	15	14000
		2000	182	3	18	16000
		2000	190	8	26	18000
		2000	186	-4	22	20000
		2000	196	10	32	22000
		2000	198	2	34	24000
		2000	199	1	35	26000
		2000	200	1	36	28000

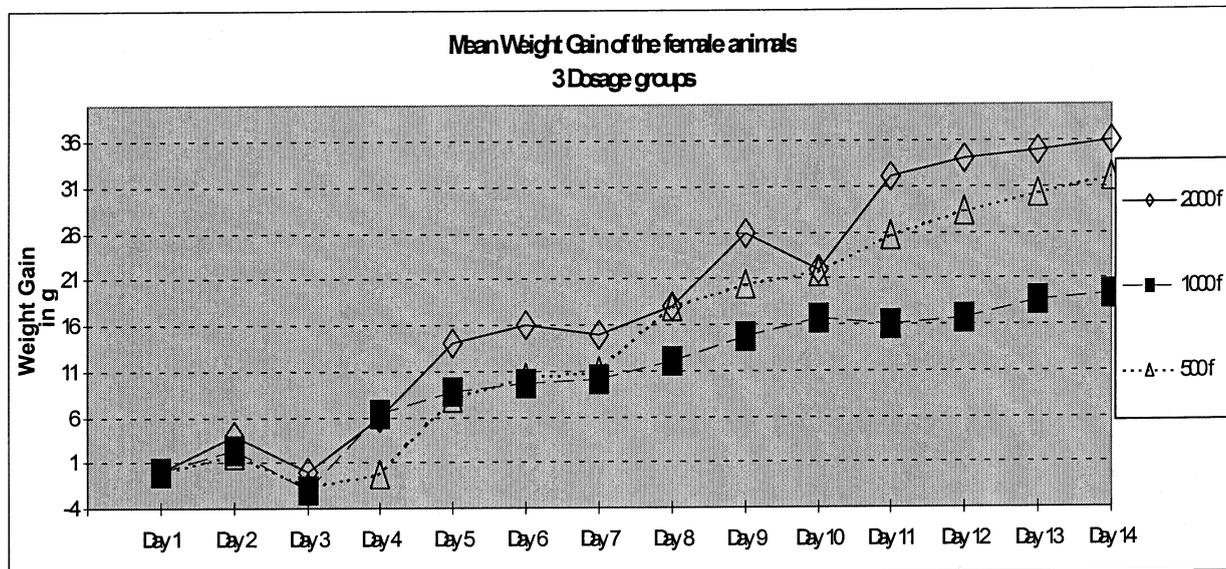
  

### Weight Development

Application	Weight (g)
1	164
2	168
3	164
4	170
5	178
6	180
7	179
8	182
9	190
10	186
11	196
12	198
13	199
14	200

**Mean Body weight development female animals:**

Mean Weight Gain Females																
001698																
Dosage	Sex	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
2000	f	0,00	4,00	0,00	6,00	14,00	16,00	15,00	18,00	26,00	22,00	32,00	34,00	35,00	36,00	
1000	f	0,00	2,33	-2,00	6,33	8,67	9,67	10,00	12,00	14,67	16,67	16,00	16,67	18,67	19,33	
500	f	0,00	2,00	-1,67	-0,33	8,00	10,33	11,00	18,00	20,33	21,67	25,67	28,33	30,33	32,00	



### *Food Consumption*

All animals showed normal food intake and no obvious reduction in food consumption was found.

### *Clinical Observation*

All rats treated with the test item WACKER BS 1701 survived throughout the test period without showing relevant clinical-toxic effects.

### *Haematology and Clinical Biochemistry*

Most values were within the expected ranges.

No relevant differences between the groups were found.

No dose dependency and toxicological relevance was found.

*Pathology*

No abnormal findings in any of the animals were observed.

## Results

In this 14-day Oral Dose Range Finding Study with the test item WACKER BS 1701 no specific compound related effects were observed.

### *Conclusions*

Considering the reported data the following doses are recommended for the 28 day Toxicity study:

Low Dose: 150 mg/kg BW  
Medium Dose: 500 mg/kg BW  
High Dose: 1000 mg/kg BW

## Distribution of the Report

Sponsor	1x (original)
Study Director	1x (copy)